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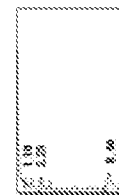
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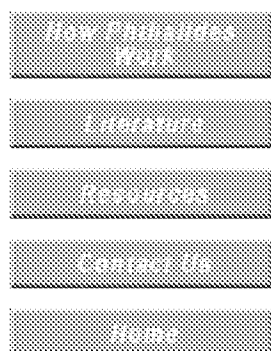
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Phthalides

From celery seeds and other botanicals



Research studies exploring Phthalides



T1: Phytotherapy Research, Vol. 11, 576—582 (1997)

Cardiovascular Pharmacology of 3-n-butylphthalide in Spontaneously Hypertensive Rats

D. Tsi and B. K. H. Tan

The hypotensive and vasorelaxant effects of 3-n-butylphthalide (BuPh) and its possible mechanisms were investigated in spontaneously hypertensive rats (SHR) for the first time. A 13-day intake of BuPh at doses of 2.0 and 4.0 mg/day produced a transient hypotensive effect while a daily dose of 0.5 mg/day showed a significant hypotensive effect only on day 12. BuPh at 0.5 mg/day had no effect on tissue angiotensin converting enzyme (ACE) activities, or on the tissue lipid peroxidation in endothelium-intact and denuded aortic rings precontracted with phenylephrine and KCl. N-methyl-L-arginine methyl ester, an inhibitor of nitric oxide synthase, did not attenuate the vasorelaxant activities. Cumulative concentration response curves of phenylephrine and Ca^{2+} (in CaCl_2 -free, high Ca^{2+} were non-competitively inhibited by BuPh. However, BuPh did not interfere with the caffeine-induced release of intracellular Ca^{2+} . It appears that the vasorelaxant effect of BuPh could be attributed to Ca^{2+} entry, possibly through voltage- and receptor-operated Ca^{2+} channels, thereby lowering blood pressure of SHR.

2: Acta Pharmacol Sin 2000 May;21(5):433-8

Inhibitory effects of chiral 3-n-butylphthalide on inflammation following focal ischemic brain

Xu HL, Feng YP.

AIM: To evaluate the degree of neutrophil infiltration into ischemic tissue after transient focal ischemia, and to examine the effects of chiral 3-n-butylphthalide (NBP) on this inflammatory response.
METHODS: After a 24-h reperfusion following transient cerebral ischemia, two different techniques, immunohistochemical analysis and modified myeloperoxidase (MPO)-quantification method, were utilized to identify

neutrophils into cerebral tissue following ischemia. The expression of intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor- α (TNF- α) in the ischemic zone were observed by immunohistochemistry, Western blot, and in situ hybridization techniques.

RESULTS: In cerebral cortex area perfused by middle cerebral artery (MCA), MPO activity increased after 24 h of reperfusion in the vehicle group, and it correlated well with the infiltrated neutrophils. Administration of dl-, d-, and l-NBP (20 mg/kg-1) partially inhibited both the increase in MPO activity and the appearance of neutrophils in ischemia-reperfusion sites. Up-regulation of ICAM-1 was observed on the microvessel endothelium in the ischemic territory. In addition, chiral NBP decreased ICAM-1 expression, and decreased the number of TNF- α blue purple-positive neurons in the ischemia-reperfusion injury. **CONCLUSION:** The results indicate that the increase in neutrophils into the infarct site implicated postischemic brain injury, and NBP was effective in protecting brain tissue sites following ischemic insult.

PMID: 11324442 [PubMed - indexed for MEDLINE]

3: Yakugaku Zasshi 1989 Jun;109(6):402-6

[Centrally acting muscle relaxant effect of phthalides (ligustilide, cnidilide and senkyunolide) from *Cnidium officinale* Makino] [Article in Japanese] Ozaki Y, Sekita S, Harada M.

The present study was carried out to elucidate a centrally acting muscle relaxant effect of a chloroform-soluble fraction and its component, namely, ligustilide, cnidilide and senkyunolide obtained from *Cnidium officinale* Makino. These three compounds were isolated from the chloroform-soluble fraction by column chromatography on silica gel. The centrally acting muscle relaxant effect was investigated by the crossed extensor reflex in anesthetized rats and these samples were suspended in 0.5% carboxymethylcellulose solution and administered i.p. These three compounds as well as the chloroform-soluble fraction depressed the reflex response. The depressive potencies among them were almost the same. The depressive potencies were also the same or somewhat weaker as that of mephenesin. As a curare-like effect was observed, a muscle relaxation induced by these phthalide compounds is considered to be of central origin. PMID: 2810059 [PubMed - indexed for MEDLINE]

4: Clin Exp Pharmacol Physiol 1999 Oct;26(10):845-6

NBPA: a cerebral ischemic protective agent.

Zhang J, Peng X, Wei G, Su D.

1. NBPA is a derivative of 3-n-butyrylphthalide isolated from *Apium granolens* Linn.
2. At concentrations ranging from 6×10^{-6} to 10^{-6} mol/L, NBPA inhibited the L-type calcium channel activity in guinea-pig myocardial cells and cultured human neuroblastoma cells.
3. At 10^{-6} mol/L, NBPA markedly inhibited calcium-dependent and -independent release of intracellular calcium.

synaptosomes.

4. The $[^{31}\text{P}]$ nuclear magnetic resonance spectrum has shown that pretreatment with NBPA improved energy metabolism.

5. In situ hybridization has shown that 10 and 20 mg/kg, i.p., NBPA prior to cerebral artery accelerate the expression of heat shock protein 70 mRNA and inhibit c-fos mRNA express

6. It has been shown that NBPA decreases the nitric oxide content and bc nitric oxide synl in the global cerebral ischaemia-reperfusion model in rats. In addition, it has been shown t significantly inhibits the expression of inducible NOS protein.

PMID: 10549420 [PubMed - indexed for MEDLINE]

5: Bioorg Med Chem 1999 Jul;7(7):1445-50

Structure-requirements of isocoumarins, phthalides, and stilbenes from

Hydrangeae Dulcis Folium for inhibitory activity on histamine release from rat

peritoneal mast cells.

Matsuda H, Shimoda H, Yoshikawa M.

We examined the structure-activity relationships of isocoumarins, phthalides and stilbenes Hydrangeae Dulcis Folium and related compounds for the inhibition of histamine release in mast cells. The activities of isocoumarins such as thunberginols A and B were more potent dihydroisocoumarins such as hydrangenol and thunberginol G. The double bond at the 3-position be essential to potentiate the activity. The hydroxyl groups at the 6-, 3'- and 4'-positions of essential for the activity, while the hydroxyl group at the 6-position was scarcely needed. 5 of benzylidenephthalides such as thunberginol F were more potent than those of hydrama the presence of a double bond at the 3-position was needed to increase the activity. More group at the 8-position was essential for the activity. On the time course study, thunbergin completely inhibited histamine release by pretreatment at 100 microM for 1 to 15 min, whe inhibited histamine release only following 1-min pretreatment at 1000 microM. These resul the mechanisms of the inhibitory effect of thunberginols are different from that of DSCG.

PMID: 10465418 [PubMed - indexed for MEDLINE]

6: Life Sci 1998;62(23):2073-82

Effects of methylenechloride-soluble fraction of Japanese angelica root extract, ligustilide and butylidenephthalide, on pentobarbital sleep in group-housed and socially isolated mice.

Matsumoto K, Kohno S, Ojima K, Tezuka Y, Kadota S, Watanabe H.

We previously showed that the extract of Japanese angelica root (JAR-E) reversed the de pentobarbital (PB) sleep induced by isolation stress and yohimbine and methoxamine, stir noradrenergic systems, in mice. Here, we tested the effects of several fractions from JAR butylidenephthalide, phthalide components of JAR-E, on PB sleep in isolated mice to elucidate mechanism of the action of JAR-E. Methanol-soluble (Met-S) and -insoluble (Met-IS) fractions from JAR-E. Methylenechloride-soluble (MC-S) and -insoluble fractions (MC-IS) were prepared. MC-S (11.4-76 mg/kg, p.o.) reversed the isolation stress-induced decrease in PB sleep, but (0.8-2.4 g/kg, p.o.) nor MC-IS (0.7-2 g/kg, p.o.) had the same effect. The i.p. administration had a similar activity to that observed after the p.o. administration of the same fraction. Ligustilide (l.p.) and butylidenephthalide (10-30 mg/kg, i.p.) reversed PB sleep decrease in isolated mice. Components (20 mg/kg, i.p.) attenuated the suppressive effects of yohimbine (30 nmol, i.c.v.) (200 nmol, i.c.v.) and a benzodiazepine inverse agonist FG7142 (10 mg/kg, i.p.) on PB sleep in mice. These results suggest the contribution of ligustilide and butylidenephthalide to the effect on PB sleep in isolated mice, and implicate central noradrenergic and/or GABA(A) systems in its components.

PMID: 9627086 [PubMed - indexed for MEDLINE]

7: Jpn J Pharmacol 1980 Feb;30(1):85-91

A newly isolated antispasmodic--butylidenephthalide.

Ko WC.

Butylidenephthalide (BdPh), ligustilide and butylphthalide were isolated and purified from *Ligusticum wallichii* Franch. Among these three, BdPh proved to be the most active in inhibiting contractions induced by prostaglandin F2 alpha, oxytocin and ACh. In studies done to compare BdPh and papaverine (Pap), guinea pig ileum, vas deferens and taenia coli were used. Because contractile responses of the ileum to agonists including ACh, K⁺ and Ba²⁺ in normal Tyrode, exogenous Ca²⁺ in high K⁺ (80 mM), Ca²⁺-free Tyrode solution, and also responses of vas deferens to norepinephrine. Thus, BdPh is a non-specific antispasmodic but weaker in papaverine. However, as the inhibitory effects of BdPh on phasic contraction (PC) and tonic contraction preparations, including depolarized and non-depolarized ileum and taenia coli, were much more pronounced than PC. It may be concluded that BdPh possesses an non-specific antispasmodic action

Pap, the mechanism of action being different from that of Pap.

PMID: 7401411 [PubMed - indexed for MEDLINE]

8. Zhongguo Yao Li Xue Bao. 1999 Oct;20(10):929-33.

PMID: 11270994 [PubMed - indexed for MEDLINE]

PMID: 12120812 [PubMed - indexed for MEDLINE]

Whitehouse M.W., Butlers, DE, Clarke M L, Rainsford K D

Inflammopharmacology, Vol 9, No 1,2, pp 201 -209 (2001)

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